Primary graft dysfunction does not lead to increased cardiac allograft vasculopathy in surviving patients

Murray H. Kwon, MD,[a] Samantha Y. Wong, MD,[a] Abbas Ardehali, MD,[a] Hillel Laks, MD,[a] Zilu K. Zhang, PhD,[b] Mario C. Deng, MD,[a] and Richard J. Shemin, MD[a]

Objective: Early injury is associated with the development of cardiac allograft vasculopathy in heart transplantation. We examined whether adult heart transplant recipients surviving primary graft dysfunction were more susceptible to the development of cardiac allograft vasculopathy than their nonprimary graft dysfunction counterparts.

Methods: A total of 857 patients who underwent heart transplantation between January 1994 and December 2008 at our institution were reviewed. Primary graft dysfunction was defined as the need for extracorporeal membrane oxygenation, open chest, or intra-aortic balloon pump placement within 72 hours of transplantation. Cardiac allograft vasculopathy was defined as ≥50% coronary artery stenosis in any vessel. Allograft survival was defined by patient death or need for retransplantation.

Results: Completed follow-up was available for 32 patients in the primary graft dysfunction group and 701 patients in the nonprimary graft dysfunction group. Mean recipient ages (56 years vs 55 years, respectively; $P = .50$) and ischemic times (220 minutes vs 208 minutes, respectively; $P = .35$) were similar. Donor age was significantly higher in the primary graft dysfunction group (38 years vs 32 years, $P = .02$). Five-year survivals for the primary graft dysfunction and nonprimary graft dysfunction groups were 46.9% versus 78.9% ($P < .001$). Conditional 5-year survivals in patients surviving the first year were 78.9% and 88.3% for the primary graft dysfunction and nonprimary graft dysfunction groups, respectively ($P = .18$). Within a 30-day postoperative period, there were more deaths in the primary graft dysfunction group (28.1% vs 2.3%, $P < .0001$) and more retransplants (6.25% vs 0%, $P = .002$). Of the patients surviving past 30 days, only 2 (8.7%) of the primary graft dysfunction patients developed cardiac allograft vasculopathy versus 144 (21.0%) in the nonprimary graft dysfunction group ($P < .001$).

Conclusions: Primary graft dysfunction was associated with lower 30-day, 1-year, and 5-year allograft survival rates. Surviving patients, however, did not show increased tendency toward cardiac allograft vasculopathy development. (J Thorac Cardiovasc Surg 2013;145:869-73)

Primary graft dysfunction (PGD) of heart allografts is a condition in which the newly transplanted organ is unable to meet the circulatory requirements of the recipient during the peri- and postoperative periods as a result of left ventricular, right ventricular, or biventricular dysfunction.[1] Unlike lung transplantation, in which PGD was defined formally and given a standard grading system in 2005 by an International Society of Heart and Lung Transplantation working group, PGD in heart transplantation has received relatively little attention.[2] Thus, despite being one of the most common causes of 30-day mortality after heart transplant, with an estimated incidence of up to 40%, there currently exists no widely accepted diagnostic criteria or definition for the disorder.[3,4] The causes of PGD are not completely understood; however, intrinsic donor organ abnormalities and recipient characteristics such as pulmonary hypertension, inadequate donor heart preservation, and/or nonspecific host-mediated inflammatory injury are implicated.[5]

Although PGD affects early survival adversely, chronic rejection known as cardiac allograft vasculopathy (CAV) is the predominant limitation to survival in heart transplantation beyond 1 year.[6] Both immune- and nonimmune-related factors remain associated with the development of CAV and it is reasonable to hypothesize that the allograft injury that leads to PGD in transplanted hearts will ultimately place the organ at heightened risk for development of CAV as well. This hypothesis is supported by abundant evidence in the lung transplantation literature regarding the relationship between PGD and the development of bronchiolitis obliterans syndrome, the corollary of chronic rejection in pulmonary allografts.[7-9] The causal relationship between cardiac PGD and the development of CAV, however, has yet to be clearly established.

From the Division of Cardiothoracic Surgery,[a] Department of Surgery, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, Calif; and Department of Biostatistics,[b] University of California, Los Angeles, Calif.

Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Feb 22, 2012; revisions received July 16, 2012; accepted for publication Sept 13, 2012; available ahead of print Oct 19, 2012.

Address for reprints: Murray H. Kwon, MD, 10833 LeConte Ave, Room CHS 62-229, Los Angeles, CA 90095 (E-mail: mkwon@mednet.ucla.edu).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2012.09.037

Abbreviations and Acronyms
CAV = cardiac allograft vasculopathy
ECMO = extracorporeal membrane oxygenation
IABP = intra-aortic balloon pump
PGD = primary graft dysfunction
UCLA = University of California at Los Angeles

The objective of this study is to discern whether patients surviving PGD in heart transplantation are subsequently at elevated risk for the development of CAV. In addition, we compare long-term allograft function and survival in patients surviving PGD versus the non-PGD cohort.

METHODS

The study was approved by the University of California at Los Angeles (UCLA) institutional review board. A total of 857 patients transplanted at UCLA Medical Center between January 1994 and December 2008 were reviewed retrospectively. Primary graft dysfunction was defined in patients who required (1) extracorporeal membrane oxygenation (ECMO), (2) open chest, and/or (3) usage of an intra-aortic balloon pump (IABP) within 72 hours of transplantation. Venoarterial ECMO was instituted via right atrial and aortic cannulation either with or without concomitant open chest. Patients who presented to the operating room with an IABP in place a priori as a result of poor native heart function were excluded because the balloon pumps were removed on postoperative day 1 by protocol to avoid the risk of bleeding during the immediate perioperative period and not because of the specific needs of the new allograft. Patients with positive donor-specific antibodies were excluded to remove hyperacute rejection as a potential cause of early graft failure from this study.

Patients underwent annual coronary angiography as part of routine surveillance after an initial baseline study around day 60 posttransplantation. Cardiac allograft vasculopathy was defined as the presence of $\geq$50% stenosis of 1 or more vessels. All donors older than the age of 40 years received coronary angiograms as part of the initial evaluation, and the presence of coronary artery disease excluded them from further consideration for nonalternate list candidates. Allograft survival was examined at 30 days, 1 year, and 5 years posttransplantation and was defined as either recipient death or the need for retransplantation. Donor and recipient ages and ischemic times were documented. Patients were followed for an average of 3.2 years after transplantation, with a range from 0 days to 13.2 years.

Continuous variables were reported as mean $\pm$ standard deviation and were compared with the Student *t* test. Categoric data were analyzed using 2×2 contingency tables, with *P* values determined by the Fisher exact test. Mortality curves were established using Kaplan-Meier (actuarial) curves, with *P* values generated by the log-rank test. Multivariable analyses were performed with the use of a proportional hazards regression model for competing risks. Two-tailed *P* values $< .05$ were considered statistically significant.

RESULTS

Of the 857 patients reviewed, 815 patients constituted the non-PGD group and 42 were identified with PGD according to the following criteria: 13 patients (30.9%) had institution of ECMO, 23 patients (54.8%) had IABP, and 6 patients (14.3%) were left with an open chest without concomitant ECMO or IABP. Open chest was utilized in conjunction with 1 or both of the other therapeutic maneuvers as follows: ECMO+IABP in 4 patients, ECMO alone in 1 patient, and IABP alone in 4 patients. These cases were classified either as ECMO in the first 2 categories and IABP in the third group. A total of 610 of the non-PGD group and 30 of the PGD group were males (74.8% vs 71.4%, $P = .59$).

The average recipient ages for the PGD and non-PGD control groups were 56 ± 13 years versus 55 ± 13 years ($P = .50$). The donor ages were 38 ± 15 years versus 32 ± 14 years ($P = .02$) for the PGD and control groups, respectively. Ischemic time was 220 ± 85 minutes versus 208 ± 66 minutes ($P = .35$) for PGD and non-PGD categories. Table 1 shows the 3 variables in multivariable analysis. When adjusting for recipient age and ischemic time, there is a 2% increase in the odds of PGD for every 1-year increase in the donor age.

We have complete follow-up on 733 patients, of whom 701 are non-PGD patients and 32 are PGD patients. Of the 23 PGD patients with allograft survival beyond 30 days, 2 developed CAV (8.7%) at an average time of 1.4 years posttransplant. Of the 684 non-PGD patients surviving past 30 days, 144 (21.0%) developed CAV at an average of 4.4 years after transplantation. The difference in incidence of CAV between the 2 groups is statistically significant ($P = .02$).

Figure 1 shows 5-year Kaplan-Meier survival curves for both PGD and non-PGD groups, respectively. Five-year survival was 78.9% versus 46.9% in the non-PGD patients versus PGD patients, respectively ($P < .001$). Corresponding survival rates at 30 days and 1 year were 97.7% versus 89.4% and 87.5% versus 56.3%, respectively. Within the immediate 30-day posttransplant period, 9 of 32 PGD patients expired compared with 16 of 701 in the control group (28.1% vs 2.3%, $P < .0001$). Two of the primary graft dysfunction patients required retransplantation compared with none in the control group (6.25% vs 0%, $P = .002$).

Conditional survival curves past the first year shown in Figure 2 were similar for both the PGD and non-PGD groups, suggesting that patients who survived the initial insult of PGD did not experience a worse long-term outcome compared with their non-PGD counterparts (78.9% vs 88.3%, $P = .182$).

DISCUSSION

Based on the hypothesis that early injury is associated with the development of CAV in cardiac transplantation, we examined whether adult heart transplant recipients surviving PGD were more susceptible to the development of CAV than their non-PGD counterparts. Although PGD in lung transplantation has been strongly associated with both diminished long-term survival as well as increased incidence of bronchiolitis obliterans syndrome,[7,10-13] the corresponding issue in cardiac allografts has not received similar scrutiny in the literature. There are no similar

TABLE 1. Multivariable analysis

Variable	Odds ratio	*P* value
Recipient age	1.00	.77
Donor age	1.02	.03
Ischemic time	1.00	.34

efforts to standardize the diagnosis of PGD in hearts as there are in lungs, and the issue of long-term survival or development of CAV has not been examined thoroughly. Although some have attempted to look at overall survival of patients with PGD managed with mechanical assist devices, they found direct comparisons difficult because of the wide array of definitions used by varying authors.[14,15]

The pulmonary allograft PGD classification system established by the International Society of Heart and Lung Transplantation in 2005 graded severity on a scale from 0 to 3 based on criteria of partial pressure of arterial oxygen to inspired oxygen ratios (P_{AO_2}/F_{IO_2}) and infiltrates on chest radiograph.[2] The goals of standardizing taxonomy were conducive to the multitude of studies examining the long-term effects of lung allograft PGD by allowing for reproducibility when discussing severity of the disease process. Because no such classification system exists for heart transplantation, we defined PGD by the following 3 criteria: (1) need for ECMO, (2) need for IABP, and/or (3) need for an open chest for decompression purposes within the first 72 hours posttransplantation. One could argue that the criteria to determine PGD should include the necessity of high perioperative inotrope doses in addition to the mechanical circulatory assist and open chest parameters used in this study. The consistent documentation of inotrope dosage and duration of therapy proved unreliable, however, with patients from the earlier time points in this study. The cutoff for high inotrope dosage is also arbitrary and there is as yet no standardized accepted level used to define PGD. Are

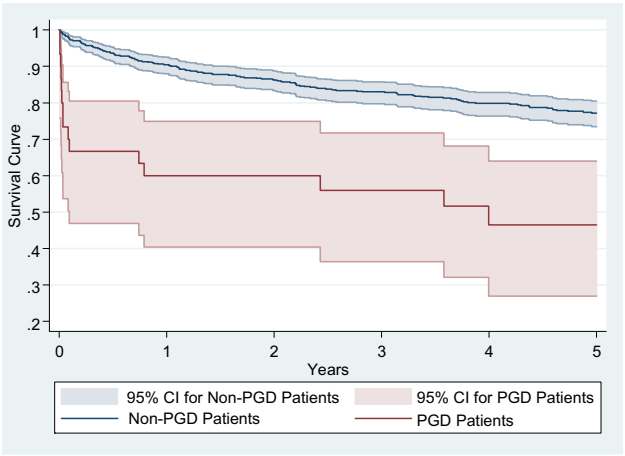

FIGURE 1. Five-year survival curves. *CI*, Confidence interval; *PGD*, primary graft dysfunction.

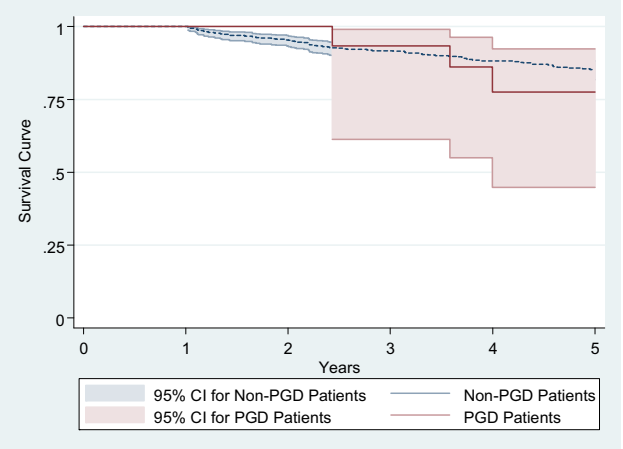

FIGURE 2. Five-year conditional survival. *CI*, Confidence interval; *PGD*, primary graft dysfunction.

numbers of inotropic agents, their dosage, or some combination of both the most relevant indicator of PGD of cardiac allografts? A recent single-institution retrospective review suggested 2 or more inotropic agents with high-dose norepinephrine or epinephrine (either >0.07 μg/kg/min) as mandatory criteria for PGD classification.[4] Although the authors are to be lauded for taking this first step, a consensus working group opinion to define and categorize this disease entity moving forward would be extremely useful.

The development of CAV is linked to immunologic and nonimmunologic factors. Primary graft dysfunction can theoretically exacerbate both etiologies through the upregulation of cytokines, leading to activation of the cellular immune system as well as localized inflammation leading to endothelial injury.[16] There is much work in animal models regarding the link between inflammation and neointimal hyperplasia characteristic of the CAV process.[17-19] There are many triggers of injury associated with PGD, including oxidative stresses, insults of myocardial stretch and/or dilation, catecholamine surges, and reactions to foreign material associated with ECMO circuits and other mechanical support devices. Left ventricular dysfunction during the early postoperative period in heart transplantation has indeed been found to correlate directly to the loss of mean luminal diameter of coronary arteries, indicative of greater CAV.[20] Our data, paradoxically, demonstrated a higher incidence of CAV in the non-PGD group.

An obvious explanation for this is that patients surviving PGD are a self-selected group, and that the sickest patients most affected by the process die early prior to the development of CAV. Most of the mortality following cardiac PGD is observed within the first postoperative month, as demonstrated by the 29% 30-day mortality in this series. The lung transplantation experience, however, is abundant with data suggesting that although recipients with PGD have high upfront mortality, surviving patients remain at heightened risk

for the long-term development of bronchiolitis obliterans and ultimate loss of graft and life.[7,21,22] One factor that may change the overall relationship between PGD and CAV in heart transplant patients over time is the increased success of mechanical circulatory support.[1] It is quite possible that, as more patients survive the initial insult as a result of advances in ECMO circuit designs, centrifugal pumps, as well as improved pharmacologic management, overall CAV incidence will increase over time.

The adverse impact of donor ischemic time on higher PGD rates is well accepted and reported in the literature. One study demonstrated that an ischemic time >300 minutes lead to a 3-fold increase in PGD.[23] These authors did not, however, find that this translated into survival differences at either the 5- or 10-year time points, and they did not look specifically at the issue of CAV development in the prolonged ischemic time group. Another group found ischemic time >240 minutes to be 1 of 6 independent variables indicating higher risk for PGD, along with recipient age $\geq$60 years, diabetes mellitus, inotrope therapy, right atrial pressure $\geq$10 mm Hg, and donor age $\geq$30 years.[4] Ischemic time in our series did not differ significantly between the PGD and non-PGD groups. Our median ischemic times were shorter than the previously mentioned studies, however, and thus this variable may not have contributed as significantly to the development of PGD in our patient population. The availability of donor organs in the Los Angeles metropolitan area may have been a factor in this regard because it lowers overall travel times for organ retrieval, keeping ischemic times shorter.

Our data did emphasize the importance of donor age in multivariable analysis when looking at the development of PGD in newly transplanted hearts. Older donors have also been implicated with poorer cardiac transplant outcomes by other institutions. Causal factors cited include decreased ability to withstand longer ischemic times as well as increased tendency toward CAV possibly because of preexisting coronary artery disease.[24]

In conclusion, PGD was associated with lower 30-day, 1-year, and 5-year survival rates. After the first year, however, there was no difference in survival between both categories, suggesting that mortality—when it occurs—is at the earlier time points and conditional survival past 1 year is the same. Although conclusions regarding CAV development must be made carefully given the relatively low number of PGD patients in this series, those patients who survived did not show an increased tendency toward CAV development. These results may prove useful when counseling patients surviving PGD with regard to their long-term risks of developing chronic rejection in the form of CAV and their overall survival in general. Unlike their lung transplant counterparts, there are no data currently to suggest that they are at heightened risk of developing chronic rejection over time.

Lastly, this study reiterates the need for formal clarification and identification of cardiac allograft PGD by means of a consensus group similar to that seen in lung transplantation. Only in this way will comparative multi-institutional studies be enabled and can subsequent advances in the identification and treatment of PGD of cardiac allografts be realized.

References

1. Iyer A, Kumarasinghe G, Hicks M, Watson A, Gao L, Doyle A, et al. Primary graft failure after heart transplantation. *J Transplant*. 2011;2011:Article ID 175768.
2. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition: a consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2005;24:1454-9.
3. Taylor DO, Stehlik J, Edwards LB, Aurora P, Christie JD, Dobbels F, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult heart transplant report—2009. *J Heart Lung Transplant*. 2009;28:1007-22.
4. Segovia J, Cosio MD, Barcelo JM, Bueno MG, Pavia PG, Burgos R, et al. RADIAL: a novel primary graft failure risk score in heart transplantation. *J Heart Lung Transplant*. 2011;30:644-51.
5. Aharinejad S, Andrukhova O, Gmeiner M, Thomas A, Aliabadi A, Zuckermann A, et al. Donor serum SMARCAL1 concentrations predict primary graft dysfunction in cardiac transplantation. *Circulation*. 2009;120:S198-205.
6. Colvin-Adams M, Agnihotri A. Cardiac allograft vasculopathy: current knowledge and future direction. *Clin Transplant*. 2011;25:175-84.
7. Daud SA, Yusen RD, Meyers BF, Chakinala MM, Walter MJ, Aloush AA, et al. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med*. 2007;175:507-13.
8. Lee JC, Christie JD. Primary graft dysfunction. *Proc Am Thorac Soc*. 2009;6:39-46.
9. Whitson BA, Prekker ME, Herrington CS, Whelan TP, Radosevich DM, Hertz MI, et al. Primary graft dysfunction and long-term pulmonary function after lung transplantation. *J Heart Lung Transplant*. 2007;26:1004-11.
10. Bermudez CA, Adusumilli PS, McCurry KR, Zaldonis D, Crespo MM, Pilewski JM, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: long-term survival. *Ann Thorac Surg*. 2009; 87:854-60.
11. Bharat A, Kuo E, Steward N, Aloush A, Hachem R, Trulock EP, et al. Immunological link between primary graft dysfunction and chronic lung allograft rejection. *Ann Thorac Surg*. 2008;86:189-95.
12. Carter YM, Davis RD. Primary graft dysfunction in lung transplantation. *Semin Respir Crit Care Med*. 2006;27:501-7.
13. Christie JD, Kotloff RM, Ahya VN, Tino G, Pochettino A, Gaughan C, et al. The effect of primary graft dysfunction on survival after lung transplantation. *Am J Respir Crit Care Med*. 2005;171:1312-6.
14. Kavarana MN, Sinha P, Naka Y, Oz MC, Edwards NM. Mechanical support for the failing cardiac allograft: a single-center experience. *J Heart Lung Transplant*. 2003;22:542-7.
15. Marasco SF, Esmore DS, Negri J, Rowland M, Newcomb A, Rosenfeldt FL, et al. Early institution of mechanical support improves outcomes in primary cardiac allograft failure. *J Heart Lung Transplant*. 2005;24:2037-42.
16. Kass M, Haddad H. Cardiac allograft vasculopathy: pathology, prevention and treatment. *Curr Opin Cardiol*. 2006;21:132-7.
17. Hsieh GR, Schnickel GT, Garcia C, Shefizadeh A, Fishbein MC, Ardehali A. Inflammation/oxidation in chronic rejection: apolipoprotein a-i mimetic peptide reduces chronic rejection of transplanted hearts. *Transplantation*. 2007;4(2):238-43.
18. Iwanaga K, Hasegawa T, Hultquist DE, Harada H, Yoshikawa Y, Yanamadala S, et al. Riboflavin-mediated reduction of oxidant injury, rejection, and vasculopathy after cardiac allotransplantation. *Transplantation*. 2007;83:747-53.
19. Tanaka M, Mokhtari GK, Terry RD, Gunawan F, Balsam LB, Hoyt G, et al. Prolonged cold ischemia in rat cardiac allografts promotes ischemia–reperfusion injury and the development of graft coronary artery disease in a linear fashion. *J Heart Lung Transplant*. 2005;24(11):1906-14.

20. Bolad IA, Robinson DR, Webb C, Hamour I, Burke MM, Banner NR. Impaired left ventricular systolic function early after heart transplantation is associated with cardiac allograft vasculopathy. *Am J Transplant*. 2006;6(1):161-8.
21. Lee JC, Christie JD. Primary graft dysfunction. *Clin Chest Med*. 2011;32:279-93.
22. Huang HJ, Yusen RD, Meyers BF, Walter MJ, Mohanakumar T, Patterson GA, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. *Am J Transplant*. 2008;8:2454-62.
23. Marasco SF, Esmore DS, Richardson M, Bailey M, Negri J, Rowland M, et al. Prolonged cardiac allograft ischemic time: no impact on long-term survival but at what cost? *Clin Transplant*. 2007;21(3):321-9.
24. Lietz K, John R, Mancini DM, Edwards NM. Outcomes in cardiac transplant recipients using allografts from older donors versus mortality on the transplant waiting list: implications for donor selection criteria. *J Am Coll Cardiol*. 2004; 43:1553-61.